Convention Application for a Patent

We, BOEHRINGER INGELHEIM G.m.b.H., a Body Corporate organised under the laws of the Federal Republic of Germany,

of Ingelheim/Rhein, Federal Republic of Germany,

hereby apply for the grant of a Patent

for an invention entitled "Substituted 4H-s-Triazolo[3,4-c]thieno-[2,3-c]1,4-diazeepines"

which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered P 28 30 782.6 for a patent or similar protection made in Federal Republic of Germany on 13th July, 1978.

Our address for service is: CALLINAN AND ASSOCIATES Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Dated this 12th day of July 1979.

BOEHRINGER INGELHEIM G.m.b.H.
By its Patent Attorneys:
CALLINAN AND ASSOCIATES
Declaration in Support of
(a) A Convention Application
(b) An Application for a Patent or Patent of Addition

In support of the Application/Convention Application made by the company
(a) BOEHRINGER INGELHEIM G.m.b.H.
for a patent/patent of addition for an invention entitled:
(d) "Substituted 4H-s-Triazolo[3,4-c]thieno-[2,3-e]1,4-diazepines"

I/we (c) Mark Joseph Callinan
of (f) 5 Dover Place, Parkdale, Victoria, Australia

I do solemnly and sincerely declare as follows:

1. (a) I am/we are the applicant(s) for the patent/patent of addition.

(b) I am/we are authorised by BOEHRINGER INGELHEIM G.m.b.H.
the applicant for the patent/patent of addition to make this declaration on its behalf.

2. (i) The basic application(s) as defined by Section 141 of the Act was/were made in the Federal Republic on the 13th day of July 1978 of Germany by C.H. BOEHRINGER SOHN.

3. (j) The said Company is entitled to make the application as follows:

The said Company would, if a patent were granted on an application made by the said actual inventors, be entitled to have the patent assigned to it and is the assignee of priority right from the aforesaid basic applicant.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

(a) Declared at Richmond, Victoria this 12th day of July 1979.
Pharmaceutical compositions having neuroleptic activity and/or antidepressive properties are also claimed.

Claim

1. Compounds of general formula

\[
\begin{align*}
&\text{\text{R}_2} & \text{\text{R}_3} & \text{\text{R}_4} & \text{\text{R}_5} \\
&\text{N} & \text{N} & \text{N} & \text{N} \\
&\text{S} & \text{C} & \text{C} & \text{C} \\
&\text{R}_2 & \text{R}_3 & \text{R}_4 & \text{R}_5
\end{align*}
\]

(wherein \(\text{R}_2\) represents a hydrogen, fluorine, chlorine or bromine atom;

\(\text{R}_3\) represents a chlorine or bromine atom or an alkyl group.

2/...
having 1 to 3 carbon atoms; and

\( R_4 \) and \( R_5 \), which may be the same or different, each represents
a hydrogen atom, an alkyl group having 1 to 4 carbon atoms
or a hydroxyalkyl group having 2 or 3 carbon atoms, or \( R_4 \) and
\( R_5 \) together with the nitrogen atom to which they are attached
form a 5- or 6-membered saturated heterocyclic ring which is option-
ally substituted by one or two methyl groups and which in the case
of a 6-membered ring may optionally contain an oxygen atom).
The following statement is a full description of this invention, including the best method of performing it known to me:—

"Substituted 4H-s-Triazolo[3,4-c]thieno-2,3-e[1,4-diazepines"

*Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.
This invention relates to novel substituted 4H-s-triazolo[3,4-c]thieno[2,3-e]1,4-diazepines having interesting pharmacological properties.

According to one feature of the invention there are provided compounds of general formula

![Molecule Diagram](image)

(wherein \( R_2 \) represents a hydrogen, fluorine, chlorine or bromine atom;
\( R_3 \) represents a chlorine or bromine atom or an alkyl group having 1 to 3 carbon atoms; and
\( R_4 \) and \( R_5 \), which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 4 carbon atoms or hydroxyalkyl group having 2 or 3 carbon atoms, or \( R_4 \) and \( R_5 \) together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated heterocyclic ring which is optionally substituted by one or two methyl groups, and which in the case of a 6-membered ring may optionally contain an oxygen atom).

As stated above the compounds according to the invention exhibit interesting pharmacological properties. In particular our tests have indicated that the compounds show a neuroleptic activity, e.g., tranquilizing, anxiolytic
and/or tensiolytic properties. Preferred compounds according to the invention, by virtue of their favourable pharmacological properties, are those in which $R_2$ represents a chlorine atom, $R_3$ represents a bromine atom, and $R_4$ and $R_5$ represent $C_1$ to $C_3$ alkyl groups or in the case of one of $R_4$ and $R_5$ represents a $\beta$-hydroxyethyl group.

Especially preferred compounds according to the invention, by virtue of their particularly favourable pharmacological properties, are the following:

- 1-dimethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine;
- 1-diethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine; and
- 1-[N-methyl-N-(\beta-hydroxyethyl)-amino]-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]thieno[2,3-e]1,4-diazepine.

Compounds according to the invention may be prepared by any of the following processes, which processes constitute further features of the invention, a) by reacting a compound of formula

$$\text{Hal}$$

$$R_3$$

$$R_2$$

(II)

(wherein $R_2$ and $R_3$ are as hereinbefore defined, and Hal represents a halogen atom) with an amine of formula
(wherein \( R_4 \) and \( R_5 \) are as hereinbefore defined); and

c) by dehydrogenating a compound of formula

(IV)

(wherein \( R_2, R_3, R_4 \) and \( R_5 \) are as hereinbefore defined); and

c) by reacting a compound of formula

(V)
(wherein \( R_2 \) and \( R_3 \) are as hereinbefore defined) with cyanogen bromide and, if desired, alkylating the product thereby obtained.

The reaction of compounds of general formula II with an amine of formula III according to process a) may be effected either with or without a solvent. Solvents which may be used include, for example, benzene, toluene, dioxan, tetrahydrofuran and halogenated hydrocarbons (such as carbon tetrachloride or methylene chloride) and the reaction is preferably effected at the boiling point of the solvent used. When the starting compound of formula III is a lower amine (e.g. dimethylamine or diethylamine) the reaction is preferably effected in an autoclave. The reaction time depends upon the particular starting materials used, and may vary from a few minutes to several hours.

Dehydrogenation of compounds of general formula IV according to process b) is generally effected in the presence of a dehydrogenation agent such as, for example, a halogen or a compound of the higher oxidation states of chromium or manganese (e.g. a chromate, dichromate or permanganate).

If the dehydrogenation is effected in the present of a halogen, a solvent is preferably present. Solvents which may be used for this purpose include, for example, halogenated hydrocarbons such as chloroform or methylene chloride. Dehydrogenation in the presence of the above-mentioned compounds of chromium or manganese is preferably effected in a solvent such as, for example, acetone, tetrahydrofuran or dioxan, and if desired in the presence of a phase transfer catalyst. According to the particular type of dehydrogenation agent used, the reaction temperature
generally lies between 0°C and the boiling temperature of the solvent used.

The reaction of a 2-hydrazino-thieno[2,3-e]1,4-
diazepine of formula V with cyanogen bromide according to process c) produces compounds of formula I in which $R_4$ and $R_5$ are hydrogen atoms, i.e.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{BrC} = \text{N} \\
\text{N} & \quad \text{N}
\end{align*}
\]

(c.f. K.T. Potts and C. Hirsch, J. Org. Chem. 33, 143 (1968)). The reaction is preferably effected in the presence of a solvent such as, for example, an alcohol, benzene, toluene or a halogenated hydrocarbon.

If desired, the compounds of general formula I may be subsequently alkylated in a conventional way. Alkylating agents which may be used for this purpose include, for example, alkyl halides, dialkyl sulfates and esters of toluenesulfonic acids. The alkylation is preferably effected in a solvent such as tetrahydrofuran, dimethylformamide or a lower alcohol, the alkylation may however also be effected without the addition of a solvent. When it is desired to introduce a hydroxyalkyl group, the
alkylating agent is preferably an alkylene oxide.

Examples of compounds of general formula I which may be readily prepared by the preceding processes, include the following:

5 8-bromo-6-(o-chlorophenyl)-1-amino-4H-s-triazol[3,4-c]-thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-methylamino-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-ethylamino-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-diethylamino-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-methyleneamino-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-n-propylamino-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-diisopropylamino-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-[N-methyl-N-ethylamino]-4H-s-triazolo[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-[N-methyl-N-(β-hydroxyethyl)amino]-4H-s-triazolo[3,4-c]thieno[2,3-e]1,4-diazepine,
8-bromo-6-(o-chlorophenyl)-1-[di-(β-hydroxyethyl)amino]-4H-s-triazolo[3,4-c]thieno[2,3-e]1,4-diazepine,
8-ethyl-6-(o-chlorophenyl)-1-dimethylamino-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine,
The starting compounds of general formula II are known compounds and have been described in the literature. Starting compounds of general formula IV may be obtained by reacting a compound of formula
(wherein \( R_2, R_3 \) and Hal are as hereinbefore defined) with an amine of formula III, under similar conditions indicated for process a), and subsequently exchanging the oxygen atom of the ring by a nitrogen atom, as described in published German Patent Application No. P 25 31 678.

As stated above, compounds of general formula I exhibit interesting pharmacological properties. In particular, our tests have indicated that the compounds exhibit tranquillizing, anxiolytic and tensiolytic properties. Thus, training tests have shown that the compounds possess a pronounced neuroleptic activity. This activity has been demonstrated according to the modified discriminated active avoidance test of Dobrin, P.B., Rhyne, Arch. Pharmacodyn. 178, 351-356 (1969).

The tests which we have effected have in particular shown that the compounds of the invention only suppress the timely avoidance actions, but have no effect on the reaction to direct shock. Such a selective effect is considered with commercial therapeutics, such as, for example chlorpromazine, to be strong evidence for neuroleptic properties (see, for example, Cook, L., Sepirvall, J., Proceedings of the Sixth International Congress of
Furthermore, we have found that this selection is especially pronounced for the compounds of the invention and that it supercedes that of commercial products.

Therefore, the compounds of the invention may be especially suitable for the reduction of psychomotor disturbances arising from irritation and/or anxiety, for example, with schizophrenia. This tranquilizing and tensiolytic effect of the compounds does not cause a disturbance of the degree of alertness.

According to a further feature of the invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of formula I according to the invention in association with a pharmaceutical carrier or excipient.

Compositions according to the invention are conveniently in a form suitable for oral, rectal or parenteral administration, such as, for example, in the form of tablets, coated tablets, capsules, syrups, emulsions, suspensions, solutions, powders, suppositories and forms adapted to provide a sustained release of active ingredient. Such forms may be prepared using excipients and methods conventional to the pharmaceutical art.

The compositions are preferably administered in an amount sufficient to provide a daily dosage of from 5 to 150 mg of said active ingredient. The compositions are conveniently in dosage unit form, whereby each dosage unit for oral administration contains from 0.05 to 50 mg, and preferably from 0.1 to 25 mg, of said active ingredient.
If desired, the compositions according to the invention may also contain one or more further pharmacologically active ingredients such as, for example, spasmyotics and β-receptor blockers.

Tablets may, for example, be obtained by admixing the active ingredient(s) with known excipients, for example, inert diluants such as calcium carbonate, calcium phosphate or lactose; disintegrants such as corn starch or alginic acid; binders such as starch or gelatin; lubricants such as magnesium stearate or talc; and/or agents for obtaining a sustained release of active ingredient(s), such as carboxypolymethylene, carboxymethyl cellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets may also consist of several layers.

Coated tablets may be produced by coating tablet cores produced analogously to tablets described above, with agents conventionally used in for tablet coatings, for example, polyvinyl pyrrolidone, shellac, gum arabic, talc, titanium dioxide and sugar. In order to obtain sustained release or to avoid incompatibilities, the core may also consist of several layers. In order to obtain sustained release, the tablet coating may additionally consist of several layers, whereby the excipients mentioned above for tablets may be used.

Syrups containing the active ingredient(s) according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerin or sugar as well as an agent improving the taste, for example, flavourings such as vanillin or orange extract. They may also contain suspension auxiliaries or thickeners, such as sodium
carboxymethyl cellulose; wetting agents, for example condensation products of fatty alcohols with ethylene oxide; or preservatives, such as p-hydroxybenzoates.

Injection solutions may be produced in a conventional manner, for example, with the addition of preservatives such as p-hydroxybenzoates, or stabilizers, such as alkali metal salts of ethylenediamine tetraacetic acid, and thereafter filled into injection vials or ampoules.

Capsules containing the active ingredient(s) may be produced, for example, by admixing the active ingredient(s) with inert carriers, such as lactose or sorbitol and thereafter filled into gelatin capsules.

Suppositories may be produced, for example, by admixing the active ingredient(s) with carriers, such as neutral fats or polyethylene glycol and/or derivatives thereof.

The following Examples serve to illustrate the preparation of compounds according to the invention and pharmaceutical compositions containing them:
Example 1

1-Dimethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine

4.5 g (0.01 mol) of 1,8-dibromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]thieno[2,3-e]1,4-diazepine are heated in an autoclave with 50 ml of dimethylamine in 150 ml of dioxan for 1 hour at 100°C. The solvent is then distilled off, and the residue is partitioned between water and methylene chloride. The methylene chloride phase is separated off, washed with water and dried over magnesium sulfate. The solution is passed through a SiO₂ column and the desired substance is eluted with methylene chloride/methanol 98:2. After distilling off solvent, the title compound is obtained from ethyl acetate. Yield 2.2 g (52 % of theory), m.p. 166 - 168°C.

Example 2

1-Dimethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine

4.2 g (0.01 mol) of 1-dimethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]thieno[2,3-e]5,6-dihydro-1,4-diazepine are dissolved in 50 ml of methylene chloride and after addition of 0.2 g of triethyl-N-benzylammonium chloride at a temperature of from 0 to 5°C, the solution is admixed with a solution of 2 g of potassium permanganate in 20 ml of acetone. After 15 minutes, sodium bisulfite solution is added and the reaction mixture is acidified with dilute sulfuric acid. The title compound is obtained from the organic phase. Yield 3.1 g (73% of theory), m.p. 165 - 167°C.

The 5,6-dihydro starting compound used in this Example was obtained as follows:

a) 20 g (53 mmol) 7-bromo-(o-chlorophenyl)-thieno[2,3-e]-
4,1-oxazepine-2-thione (prepared analogously to the description of Belgian Patent Specification No. 844 170) are stirred in 600 ml of methylene chloride with 12 g of formyl hydrazide and 80 ml of pyridine for 45 minutes at room temperature. 10 g of POCl₃ in 50 ml methylene chloride are then added dropwise at a maximum temperature of 35°C and the reaction mixture is stirred under reflux for 5 hours. After cooling, the organic phase is shaken with 200 ml of 2 N hydrochloric acid and washed with water. After drying, the organic phase is evaporated and the residue is taken up in hot ethyl acetate. After cooling, 15 g (73% of theory) of 8-bromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]-thieno[2,3-e]4,1-oxazepine are yielded, m.p. 176 - 178°C.

b) 28 g of the compound from a) above are admixed with 5.4 ml of bromine in 280 ml of methylene chloride and 8.9 ml of pyridine. The reaction mixture is refluxed for 3 hours. After cooling, it is shaken with water, and the organic phase is dried with magnesium sulfate. The solution is then evaporated and the residue is passed through SiO₂. 19.2 g (57% of theory) of 1,8-dibromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]thieno[2,3-e]4,1-oxazepine of m.p. 138°C, are obtained.

c) 9.2 g (0.02 mol) of the dibromo compound from b) above are heated in an autoclave with 300 ml of dioxan and 100 ml of dimethylamine for 1 hour at 100°C. After distilling off the solvent, the residue is dissolved in methylene chloride, washed with water, and the organic phase dried over magnesium sulfate. A residue is obtained of 1-dimethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]thieno[2,3-e]4,1-oxazepine as an oil (7.0 g, 82% of theory).

d) 8.5 g (0.02 mol) of the oxazepine obtained in c) above
are stirred with 50 ml of conc. hydrobromic acid for 1 hour at room temperature. The reaction mixture is diluted with 200 ml of water, made alkaline with ammonia and shaken with 100 ml of methylene chloride. The methylene chloride solution is separated and then stirred with 4 ml of thionyl chloride for 1 hour. Excess thionyl chloride is decomposed carefully with water and dilute ammonia, and the organic phase is separated. After evaporation and addition of ether, 4.8 g (92% of theory) of 3-dimethylamino-4-[3-(o-chlorophenylbromomethyl)-5-bromo-thienyl-(2)]-5-chloromethyl-1,2-4-triazole of m.p. 203°C are obtained.

e) 5.3 g (0.01 mol) of the triazole from d) are heated in an autoclave with 100 ml of methanol saturated with ammonia at 60°C for 30 minutes. The reaction mixture is evaporated and worked up. A yield of 2.8 g (66% of theory) of 1-dimethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]-thieno[2,3-e]5,6-dihydro-1,4-diazepine of m.p. 155 - 157°C, is obtained.

Example 3

l-Amino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo[3,4-c]-thieno[2,3-e]1,4-diazepine

5 g (0.013 mol) of 2-hydrazino-5-(o-chlorophenyl)-7-bromo-thieno[2,3-e]1,4-diazepine are heated with 100 ml of ethanol, 1.4 g of cyanogen bromide and 1.4 g of sodium carbonate for 30 minutes at 60°C. The reaction mixture is evaporated, and the residue is dissolved in methylene chloride and chromatographed over SiO₂. The title compound is obtained in a yield of 1.5g (29% of theory), m.p. 251 - 252°C (from ethanol).
Example 4

1-Dimethylamino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine

395 mg 1-amino-8-bromo-6-(o-chlorophenyl)-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine are refluxed with 5 mmol of 85% formic acid and 2 mmol of 30% formalin solution for 15 hours. After cooling, the reaction mixture is shaken with methylene chloride. The organic phase is evaporated and the residue chromatographed over a silica gel column.

From the eluates obtained, 250 mg of the title compound of m.p. 164 - 166°C (60% of theory), is obtained.
Analogously to Examples 1 to 4, the following final products were obtained:

<table>
<thead>
<tr>
<th>Example No.</th>
<th>-N&lt;sup&gt;R&lt;sub&gt;4&lt;/sub&gt;&lt;/sup&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>m.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>-HN-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Cl</td>
<td>Br</td>
<td>166 - 168</td>
</tr>
<tr>
<td>6</td>
<td>-HN-C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>Cl</td>
<td>Br</td>
<td>224 - 226</td>
</tr>
<tr>
<td>7</td>
<td>-N(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cl</td>
<td>Br</td>
<td>143 - 145</td>
</tr>
<tr>
<td>8</td>
<td>-N&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Cl</td>
<td>Br</td>
<td>224 - 226</td>
</tr>
<tr>
<td>9</td>
<td>-N&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Cl</td>
<td>Br</td>
<td>205 - 207</td>
</tr>
<tr>
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<td>Cl</td>
<td>Br</td>
<td>175 - 176</td>
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<tr>
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<td>Br</td>
<td>180</td>
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<tr>
<td>12</td>
<td>-N</td>
<td>Cl</td>
<td>Br</td>
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</tr>
<tr>
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<td>Cl</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>130 - 132</td>
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<td>Cl</td>
<td>Cl</td>
<td>154 - 155</td>
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<td>15</td>
<td>-N(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>Br</td>
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<td>Br</td>
<td>Br</td>
<td>171</td>
</tr>
<tr>
<td>17</td>
<td>-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Cl</td>
<td>Br</td>
<td>148 - 150</td>
</tr>
</tbody>
</table>
Example A: Coated Tablets

1 tablet core contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient according to the invention</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>lactose</td>
<td>28.5 mg</td>
</tr>
<tr>
<td>corn starch</td>
<td>19.0 mg</td>
</tr>
<tr>
<td>gelatin</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td></td>
<td>50.0 mg</td>
</tr>
</tbody>
</table>

A mixture of the active ingredient with lactose and corn starch is granulated with a 10% aqueous gelatin solution through a screen of 1 mm mesh-size, dried at 40°C and triturated once more through the screen. The granulate thus obtained is admixed with magnesium stearate and pressed. The cores thus obtained are covered with a coating in the usual way, the coat being applied as an aqueous suspension of sugar, titanium dioxide, talc and gum arabic. The finished coated tablets are polished with beeswax.

Final weight of coated tablet: 100 mg.

Example B: Tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient according to the invention</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>lactose</td>
<td>50.0 mg</td>
</tr>
<tr>
<td>corn starch</td>
<td>43.5 mg</td>
</tr>
<tr>
<td>soluble starch</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>1.0 mg</td>
</tr>
<tr>
<td></td>
<td>100.0 mg</td>
</tr>
</tbody>
</table>

The active ingredient and magnesium stearate are granulated with an aqueous solution of the soluble starch, the granulate is dried and admixed thoroughly with lactose.
and corn starch. The mixture is pressed into tablets of 100 mg weight, each tablet containing 0.5 mg of active ingredient.

**Example C: Suppositories**

1 suppository contains:
- Active ingredient according to the invention 5.0 mg
- Suppository mass 1695.0 mg

The final pulverised active ingredient is stirred with an immersion homogenizer into the molten suppository mass cooled to 40°C. At 35°C the mass is poured into slightly pre-cooled moulds.

**Example D: Ampoules (Injection Solution)**

Composition:
- Active ingredient according to invention 0.5 parts by weight
- Sodium pyrosulfite 1.0 part by weight
- Disodium salt of ethylenediamine tetraacetic acid 0.5 parts by weight
- Sodium chloride 8.5 parts by weight
- Double distilled water ad 1000.0 parts by weight

The active ingredient and excipients are dissolved in a sufficient quantity of water and brought to the desired concentration with the required quantity of water. The solution is filtered and filled into 1 ml ampoules under aseptic conditions. Finally the ampoules are sterilized and sealed. Each ampoule contains 0.5 mg of active ingredient.
The claims defining the invention are as follows:

1. Compounds of general formula

\[ \text{RS}_0 \text{g}(\text{where } R_2 \text{ represents a hydrogen, fluorine, chlorine or bromine atom;}) \]

\[ R_3 \text{ represents a chlorine or bromine atom or an alkyl group having 1 to 3 carbon atoms; and} \]

\[ R_4 \text{ and } R_5, \text{ which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 4 carbon atoms} \]

\[ \text{or a hydroxyalkyl group having 2 or 3 carbon atoms, or } R_4 \text{ and } R_5 \text{ together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated heterocyclic ring which is optionally substituted by one or two methyl groups and which in the case of a 6-membered ring may optionally contain an oxygen atom).} \]

2. Compounds as claimed in claim 1 wherein \( R_2 \) represents a chlorine atom;

\[ R_3 \text{ represents a bromine atom; and} \]

\[ R_4 \text{ and } R_5 \text{ represent alkyl groups having 1 to 3 carbon atoms or one of } R_4 \text{ and } R_5 \text{ represents a } \beta \text{-hydroxyethyl group and the remaining } R_4 \text{ or } R_5 \text{ radical is an alkyl group having 1 to 3 carbon atoms.} \]

3. 1-Dimethylamino-8-bromo-6-(6-chlorophenyl)-4H-s-triazolo-
4. 1-Diethylamino-8-bromo-6-(α-chlorophenyl)-4H-s-triazolo-[3,4-c]thieno[2,3-e]1,4-diazepine.

5. 1-[N-methyl-N-(β-hydroxyethyl)-amino]-8-bromo-6-(α-chlorophenyl)-4H-s-triazolo[3,4-c]thieno[2,3-e]1,4-diazepine.

6. Compounds of general formula I as defined in claim 1 as herein specifically disclosed with the exception of the compounds claimed in any one of claims 3 to 5.

7. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula

\[ \text{Hal} \]
\[ \text{R}_3 \]
\[ \text{S} \]
\[ \text{N} \]
\[ \text{R}_2 \]

(wherein \( \text{R}_2 \) and \( \text{R}_3 \) are as defined in claim 1 and \( \text{Hal} \) represents a halogen atom) with an amine of formula

\[ \text{HN} \]
\[ \text{R}_4 \]
\[ \text{R}_5 \]
8. A process for the preparation of compounds of general formula I as defined in claim 1, which comprises dehydrogenating a compound of formula

\[
\text{(IV)}
\]

(\text{wherein } R_2, R_3, R_4 \text{ and } R_5 \text{ are as hereinbefore defined}).

9. A process for the preparation of compounds of general formula I as defined in claim 1, which comprises reacting a compound of formula

\[
\text{(V)}
\]
(wherein \( R_2 \) and \( R_3 \) are as defined in claim 1) with cyanogen bromide and, if desired, alkylation the product thereby obtained.

10. A process for the preparation of compounds of general formula I as defined in claim 1 substantially as herein described in any one of Examples 1 to 17.

11. Compounds of general formula I as defined in claim 1 whenever prepared by a process as claimed in any of claims 7 to 10.

12. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as defined in claim 1 in association with a pharmaceutical carrier or excipient.

13. Compositions as claimed in claim 12 in the form of dosage units for oral administration wherein each dosage unit contains from 0.05 to 50 mg of said active ingredient.

14. Compositions as claimed in claim 11 substantially as herein described in any one of Examples A to D.

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